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Tricho-Hepato-Enteric Syndrome: Further Delineation of a Distinct Syndrome With Neonatal Hemochromatosis Phenotype, Intractable Diarrhea, and Hair Anomalies

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We report on two sibs with syndromal congenital iron storage disease. Prenatal symptoms were IUGR, hydramnios, and placental hyperplasia. Clinical anomalies included hypertelorism and sparse, thin, curly hair (trichomalacia). Clinical course was marked by intractable diarrhoea, with normal histological and enzymological studies, cholestatic jaundice, hepatomegaly appearing after 30 days, and progressive liver failure, leading to death after a few months. The only metabolic anomaly was progressive hypermethioninemia. Pathologic examination of both children showed a similar pattern of multivisceral iron deposit compatible with a diagnosis of neonatal hemochromatosis: extensive liver fibrosis or cirrhosis with nodular regeneration, cholestasis, ductular proliferation, and hepatic, pituitary, thyroidal, adrenal, and pancreatic iron deposition. The unusual course for neonatal hemochromatosis in both sibs combined with concordant extrahepatic anomalies suggest that they could have a specific iron storage syndrome with possible autosomal recessive inheritance, probably similar to the sibship reported by Stanckler et al. [Arch Dis Child, 57:212–216, 1982]. Am. J. Med. Genet. 68: 391–395, 1997. **© 1997 Wiley-Liss, Inc.**

KEY WORDS: neonatal hemochromatosis; iron storage disease; hair anomaly; intractable diarrhea; recessive inheritance

INTRODUCTION

Neonatal hemochromatosis (NH) is an uncommon, usually lethal disorder of infancy. It is defined as a liver disease of prenatal onset, with a progressive polyvisceral iron overload topographically similar to the adult onset chromosome 6-linked hemochromatosis. NH is not associated with other birth defects, but heterogeneity is suspected, even though no specific metabolic disorder is established in most cases. Intractable diarrhoea is defined as persistent diarrhoea despite protracted bowel rest, requiring long-term parenteral nutrition in children who do not have a diagnosis that would lead to effective treatment. It is causally heterogeneous and clinically variable, but usually not associated with extradigestive anomalies. We report here on two sibs who presented with a histologically typical iron storage disorder associated with intractable diarrhoea, and other anomalies, suggesting presence of a new MCA syndrome.

CLINICAL REPORTS

Patient 1

This girl was born at 34 week of pregnancy. Caesarean section was prompted by a worsening of IUGR first detected during the 5th month. A large placenta was noted at ultrasonography. BW was 1,410 g (<10th centile), BL 38 cm (< 10th centile) and OFC 28.6 cm (<10th centile). The child was initially fed parenterally. The first trial of enteral nutrition resulted in a watery, sodium-rich diarrhoea that never resolved, despite feeding trials with protein hydrolysate formulas (Alfare, Nestlé, or similar) after several weeks of bowel rest. Facial anomalies included large, square forehead, hypertelorism with downslanting palpebral fissures, upturned nose with large tip, long philtrum, small mouth, and somewhat low-set ears (Fig. 1). Abnormal hair texture and pattern (sparse on frontal and temporal areas) were obvious from birth. Neurologically, the infant was grossly normal. Echocardiography showed an ASD, ostium secundum type. Cholestatic jaundice and hepatomegaly, first noted at day 70, were initially attributed to long-term exclusive parenteral nutrition. Icterus worsened progressively although transaminase

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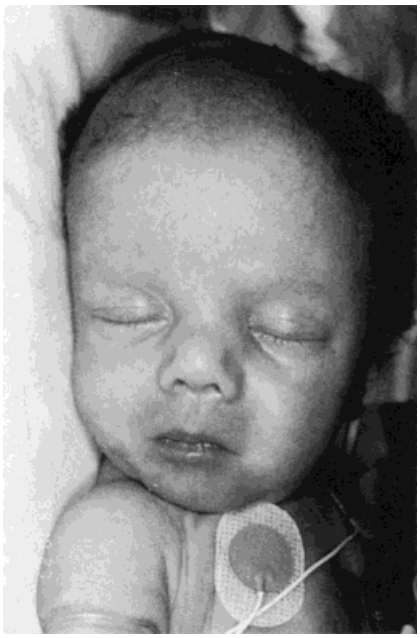

Fig. 1. Facial appearance of patient 1 at age 2 months: large forehead, broad basis of the nose, and sparse hair.

levels remained normal. Liver needle biopsy at day 135 showed extensive confluent necrosis with reticuline collapse, fibrosis, and nodular regeneration. Severe cholestasis and ductular proliferation were present with a moderate mononuclear infiltrate and a few multinucleated giant hepatocytes. The child became progressively worse and died at age 6 months of liver failure and septicemia.

Pathological investigations. At necropsy, a macronodular cirrhosis and normal extrahepatic ducts were noted. Microscopic examination confirmed an extensive liver fibrosis with prominent nodular regeneration, severe bilirubinostasis with cholestatic rosettes, ductular proliferation, multinucleated giant hepatocytes, and mild extramedullary hematopoiesis. Perl's stain showed severe iron depositions involving predominantly the hepatocytes and, in a lesser extend, Kupffer cells, biliary epithelium, and portal macrophages. Ultrastructural analysis confirmed major metabolic dysfunction with severe siderosis. Extrahepatic parenchymal iron deposition was found in thyroid, adrenal cortex, pancreas, and pituitary glands. Langerhans islets were hyperplastic. Kidneys were normal. Spleen and lymph nodes were not examined.

Metabolic investigations. These showed progressive hypermethioninaemia. First assessed at age 100 days, it reached 67 mmol/L at day 160. No other significant abnormalities of the amino acid profile were present. Hereditary tyrosinosis was ruled out by normal serum tyrosine and absence of succinylacetone and aminolevulinic hypersecretion after phenylalanine loading test. Peroxysomal disorders, homocystinuria, α-1-antitrypsin deficiency, galactosemia, hemolytic anaemia, and cystic fibrosis were also excluded, as were Infections by EBV, CMV, or hepatitis A, B, or C and syphilis. Bile acid synthesis was not investigated. Protein C and antithrombin III levels were repeatedly low. Hypereosinophilia, low IgM and high IgG were present during the first month. However, immunologic findings were normal for age, including bone marrow aspirate and lymphocyte typing, except for a low absolute and relative lymphocyte B population (9% of CD19-positive cells).

Barium swallow, duodenal, and rectal biopsies with histoenzymatic studies of lactase, sucrase, and maltase showed normal results; in particular, there was no villous atrophy. Microscopic examination of the hair and skin showed orthokeratotic hyperkeratosis and multiangulated hair shaft evocative of trichomalacia, without trichothiodystrophy (trichomalacia is usually observed in trichotillomania and is not observed in syndromal associations). Karyotype, skeletal survey, audition testing, fundi, and EEG were normal.

Patient 2

Despite restrictive genetic counselling, the parents had a second boy who was born at 37 weeks of a gestation marked by IUGR and large placenta (no histological examination). BW was 1,860 g, BL was 42 cm, and OFC was 30.9 cm (all $<$ 10th centile). He had similar hair abnormalities and facial appearance as his sister. Hepatic dysfunction was present at birth, with a very high α-foetoprotein level (5.5 g/L). He had mild and delayed hypermethioninemia (reaching 9.6 mmol/dl at day 60). As in his sister, it was never possible to establish enteric nutrition because of intractable diarrhoea. A mild cholestasis persisted from birth, with a total bilirubin level below 10 mg/dl to the 60th day and mild increase of the transaminases. Serum iron levels were repeatedly found high normal (maximum 125 mg/dl), ferritin was very high (maximum 1,027 mg/ml), and transferrin was low (maximum 104 mg/dl) and fully saturated. MR imaging confirmed liver iron overload contrasting with normal splenic content. Psychomotor development was considered normal. Because of relentless worsening of hepatic function, an orthotopic liver transplantation was performed at age 5 months. The child died 20 days later of a generalised CMV infection with hepatitis.

Pathological investigations. Liver biopsy at 6 weeks, histological examination of the liver after removal for transplantation, and necropsy were consistent with the clinical diagnosis of congenital hemochromatosis. Liver biopsy performed at 6 weeks disclosed a similar pattern as in his sister (Fig. 2): parenchymal necrosis with cirrhosis, bilirubinostasis, and ductular proliferation. Both iron and copper overload were demonstrated in hepatocytes. Iron overload was more prominent in bile ductules, whereas there was no iron overload in bile ducts. Ultrastructural examination showed normal peroxisomes. The pancreas showed marked iron deposition in the epithelial cells of the acini, and, to a less extent, in the Langerhans cells, but not in heart and thyroid. Moderate iron overload was also present in adrenal cortex and distal collecting tubules of kidneys. In the lungs, numerous macrophages loaded with hemosiderin were seen in alveolar

spaces. No iron overload was observed in spleen, thyroid, and heart. The liver graft parenchyma showed extensive panlobular necrosis, as classically observed in fulminating hepatitis. No iron overload was noted in the graft. In situ hybridisation for EBV early nuclear antigen was negative, but difficult to appreciate in the context of necrosis and cholestasis. In addition, CMV inclusions and *Pneumocystis carinii* colonies were found in the lungs (confirmed by Grocott staining and immunohistochemistry). Small intestine showed villous atrophy. The mucosa of small bowel and colon showed nuclear inclusions suggestive of a CMV infection, although immunoperoxidase staining failed to reveal CMV nuclear antigen. Target nuclei were also present in the colic mucosa.

Metabolic investigations. All investigations listed for patient 1 were repeated in patient 2, with similar negative results.

Family History

The parents, originating from Italy, were non-consanguineous and healthy. Before their two affected children, they had three miscarriages of unknown cause in the first trimester. Their chromosomes were normal. Family history was non-contributory. Liver function and basal iron metabolism testing (serum iron, transferrin, ferritin, and total iron binding capacity) were normal in both parents, except for low iron saturation capacity (14%) in the mother.

DISCUSSION

Neonatal hemochromatosis (NH) is a clinicopathological entity (i.e., a phenotype) with still undefined genetic and/or environmental (viral or toxic) bases, observed in the context of an early rapidly progressive hepatic failure with usually normal or low transaminase and high α-foetoprotein levels in the absence of obvious primary defect, but often with hypersaturated hypotransferrinemia [Witzleben and Uri, 1989; Hoogstraeten et al., 1990; Silver et al., 1989; Barnard and Manci, 1991; Knisely, 1992]. At least 65 patients with NH have been observed. The most important characteristics are a high prevalence of prematurity, IUGR, onset of the liver dysfunction within the first 2 days, and a fulminating course leading usually to death before 1 week [Knisely et al., 1987; Knisely, 1992; Barnard and Manci, 1991]. Histologically, NH is characterised by striking iron deposition in hepatocytes and, to a milder degree, in Kupffer cells and biliary epithelium, diffuse hepatic fibrosis, cholestasis, and ductular proliferation [Lee, 1994; Searle et al., 1994]. Iron overload is observed in exocrine glands, adrenal cortex, renal tubules, and thyroid follicles, but the reticuloendothelial system (spleen, lymph nodes, and bone marrow) is relatively spared.

Exceptionally, NH is diagnosed beyond the perinatal period [Barnard and Manci, 1991]. Longer survivals were reported recently in early onset cases, due to more effective intensive care or desferioxamine chelation [Knisely et al., 1989a; Jonas et al., 1987], although the only curative treatment remains orthotopic liver transplantation [Rand et al., 1992; Hayes et al., 1992]. Some

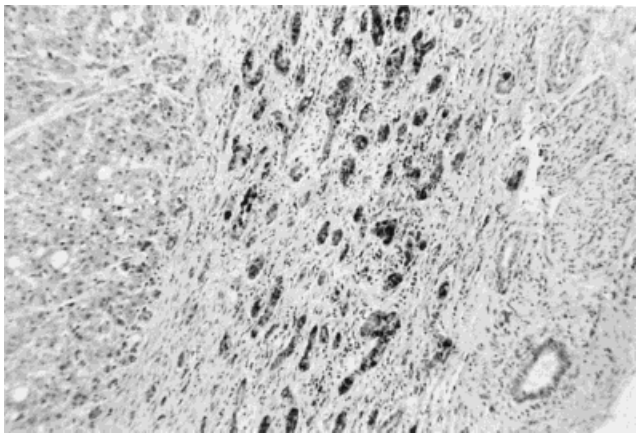

Fig 2. Patient 2: Liver biopsy: ductular proliferation with hemosiderin (dark granules). On the left appears the border of a cirrhotic nodule, with only a small amount of hemosiderin. A duct devoid of hemosiderin is seen in the lower right corner (Perls staining, original magnification: ×130).

sibs of typical cases show a milder course and survive without graft [Colletti and Clemmons, 1988; Jacknow et al., 1983; Witzleben and Uri, 1989; Hayes et al., 1992]. Nevertheless, those milder cases were perinatally symptomatic.

NH is causally heterogeneous. A significant number of cases of NH is sporadic. In can be observed with trisomy 21. Recurrence was reported at least in 24 sibships, in a pattern compatible with autosomal recessive inheritance [Becich et al., 1991; Colletti and Clemmons, 1988; Cottier, 1957; Dalhoj et al., 1990; de Boissieu et al., 1990; Dible et al., 1954; Driscoll et al., 1988; Ehrlich and Ratner, 1955; Fienberg, 1960; Hayes et al., 1992; Hoogstraeten et al., 1990; Jacknow et al., 1983; Jonas et al., 1987; Knisely et al., 1989b; Laurendeau et al., 1961; Rand et al., 1992; Silver et al., 1987; Witzleben and Uri, 1989]. In familial reports, parental consanguinity was never mentioned. NH was reported briefly in half-sibs with different fathers in two pedigrees [Jacknow et al., 1983; Knisely, 1992], and we have observed two other sets of affected half-sibs [Verloes et al., 1996].

Histological appearance of the liver in both children is clearly consistent with NH, a diagnosis further sustained by polyvisceral iron overload in the absence of hemolytic disorder and proven lack of reticuloendothelial overload in case 2. The iron overload of biliary ductules, in case 2, was unusual but not incompatible with the diagnosis of NH. Although the slowly progressive liver disease is of antenatal onset (as reflected by raised α-foetoprotein in case 2), it became symptomatic after a long "silent" period. The liver failure was delayed. The timing in the clinical history is thus very atypical for NH, although the manifestations of progressive liver insufficiency, and the lack of infectious agent or metabolic anomaly are similar to what is observed in the "classical" perinatal form. Although hypermethioninemia could be secondary to liver dysfunction and to parenteral nutrition, the importance of the plasma value of MET even at the beginning of the disorder (in case 1)

does not allow us to rule out a primary metabolic anomaly in our patients, and high α-foetoprotein levels were noted too early to incriminate total parenteral nutrition in the pathogenesis of the disorder. Hypermethioninemia occurs in hepatic failure but is usually associated with hypertyrosinemia. We did not find specific description of aminogram anomalies in NH, probably because the severity of liver dysfunction since birth makes amino acid profiles not interpretable.

A family of three sibs with recurrent lethal "neonatal hepatitis" of unknown origin was reported [Perry et al., 1965]. The disease started between 2 and 8 weeks, and the three sibs died before 12 weeks. The livers of those children were of normal weight. Microscopically, they showed fibrosis and iron deposit in hepatocytes but not in Kupffer cells, very enlarged kidneys with marked tubular ectasia, Langerhans cell hyperplasia, and lymphoid hypoplasia. A 50-fold increase of serum MET over the mean at birth, and a 10-fold increase of TYR were measured in one child. Following the authors, the degree of increase in MET was entirely out of proportion to that of other amino acids and not associated with a generalised hyperaminoacidemia. The authors favored a primary defect of MET metabolism in those children. Considering the brief histological description, those sibs could have had a subacute form of NH comparable to our cases, but tyrosinemia was not excluded.

Chronic diarrhoea, minor facial anomalies, and hair anomalies have not been recorded previously with NH. Except for a child with facial anomalies, complex cyanotic heart disease, syndactyly, and post-axial polydactyly [Castillo Taucher et al., 1994], no case of NH to date has been reported with other birth defects.

Two sibs were described [Stankler et al., 1982] with an association strikingly similar to that seen in our patients. The authors described two small-for-date babies (1,680 and 1,620 g at term) with large placenta, prominent eyes, flat, broad nose, large mouth, large, low-set ears, and progressive failure to thrive. Both developed intractable watery diarrhoea in the third week of life, which caused their death at day 33 and 87, respectively. No explanation was found for this intestinal dysfunction. High methionine levels were observed in one child (up to 20 mg/100 ml), whereas tyrosine levels were high at time of Guthrie test but normal later. At necropsy, fibrosis and cirrhosis of the liver were noted, with bile duct proliferation, presence of some giant cells, and extensive necrosis in one. "Hemosiderosis" of the liver and exocrine pancreas and thymus, as well as an increased number of Langerhans islets were observed in both sibs. Splenic iron deposition was mentioned in one. Although the term "hemochromatosis" does not appear in the article (a possible reason for this paper not to be quoted in the hemochromatosis literature), the description of the authors fits this diagnosis. The histology of the small intestine was normal in both children. Sparse microcysts of the distal collecting tubule were observed in one. Both children had woolly, easily removed hair with tortuosities (pili torti), aniso- and poikilotrichosis, trichoschisis, trichorrhexis, and longitudinal breaks. Under scanning electron microscopy, their aspect was felt unique ("trichorrhexis blastysis"). Biochemical analysis of the hair showed several anomalies of the aminoacid pattern, including low cystine content.

These two patients appear strikingly similar to our cases, including the facial anomalies. Although we do not perform electron micrography and amino-acid studies of the hair of our cases, their twisted aspect is similar. Recently, a syndrome of intractable diarrhoea, immunodeficiency, and dysmorphism [Girault et al., 1994] was described, in which diarrhoea is associated with low birth weight, prominent forehead and cheeks, hypertelorism, pale, woolly, brittle hair with trichorrhexis nodosa, erythrodermia, unclassifiable combined immunodeficiency with high IgA levels, and mental retardation. Biliary cirrhosis developed in some. Contrary to our patients, this syndrome shows severe villous atrophy. Cirrhosis was observed in two cases treated respectively 26 and 58 months by total parenteral nutrition, and was considered a complication of the therapy. Hemochromatosis was not mentioned. Despite some similarities with Stankler's patients and our cases, the absence of early liver disease, the severe villous atrophy and the immune anomalies do not allow to lump Girault's cases with ours at this moment, although heterogeneity cannot be ruled out.

In summary, the two sibs reported here have a clinically atypical, but pathologically typical NH, associated with unusual extrahepatic defects. They are likely to have the same disorder as the patients reported by Stankler et al. in 1982. They represent a separate nosologic entity within the frame of NH phenotype, with probable autosomal recessive inheritance, for which we suggest the name tricho-hepato-enteric syndrome. Dysmorphologenetic aspects, hair anomaly, and aminoacid metabolism should be (re)assessed in other cases of atypical NH, and relationships of this syndrome with the disorder reported by Girault et al. should be sorted out in further cases.

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